Immunotherapy for NSCLC
management of toxicities in practice

Karim Vermaelen, MD PhD
TOGA Spring Meeting 2018

Mild checkpoint inhibitor rash
Can be treated with topical corticosteroids

Diarrhea and Colitis
Slangen et al., World J Gastrointest Pharmacol Ther, 2013

Pneumonitis
Two doses of ipilimumab and four of nivolumab
Toxicity of immune checkpoint blockade … should not come as a surprise

- PD1 gene-deficient mice have an auto-immune phenotype
  - cardiomyopathy
  - arthritis
  - glomerulonephritis

H. Nishimura et al, Immunity 1999

- Human PD1 gene polymorphisms are associated with auto-immune diseases
  - 30 SNPs in human PD1 gene
  - associated with SLE, RA, psoriasis
Toxicity of immune checkpoint blockade
... should not come as a surprise

PD-L1 regulates a critical checkpoint for auto-immune myocarditis and pneumonitis (preclinical mouse model)

J. Lucas et al, J Immunol 2008
Toxicity of immune checkpoint blockade
organ systems at risk

- Hypophysis
- Encephalitis
- Uveitis and orbital inflammation
- Dry mouth
- Hypothyroidism
- Pneumonitis
- Myocarditis
- Adrenal insufficiency
- Nephritis
- Rash and vitiligo
- Enterocolitis
- Pancreatitis and auto-immune diabetes
- Cytopenia
- Arthralgia
Toxicity of immune checkpoint blockade data from phase 3 anti-PD1 trials

-grade 3-4-5 toxicity-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>nivo SQ</th>
<th>nivo non-SQ</th>
<th>pembro</th>
<th>atezo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

J. Brahmer et al, NEJM July 2015
H. Borghaei et al, NEJM October 2015
R. Herbst et al, The Lancet December 2015
A. Rittmeyer et al, The Lancet January 2017
## Toxicity of immune checkpoint blockade data from phase 3 anti-PD1 trials

<table>
<thead>
<tr>
<th></th>
<th>CHECKMATE-017 squamous</th>
<th>CHECKMATE-057 non-squamous</th>
<th>KEYNOTE-010 both histologies</th>
<th>OAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>immunotherapy vs comparator</td>
<td>nivolumab vs docetaxel</td>
<td>nivolumab vs docetaxel</td>
<td>pembrolizumab vs docetaxel</td>
<td>atezolizumab vs docetaxel</td>
</tr>
<tr>
<td>all treatment-related AEs (%)</td>
<td>61% vs 87%</td>
<td>71% vs 88%</td>
<td>63% vs 81%</td>
<td>64% vs 86%</td>
</tr>
<tr>
<td>toxicity grade 3 or higher</td>
<td>7% vs 55%</td>
<td>10% vs 54%</td>
<td>13% vs 35%</td>
<td>15% vs 43%</td>
</tr>
<tr>
<td>discontinuation rate</td>
<td>6% vs 10%</td>
<td>6% vs 15%</td>
<td>4% vs 10%</td>
<td>8% vs 19%</td>
</tr>
</tbody>
</table>

J. Brahmer et al, NEJM July 2015  
H. Borghaei et al, NEJM October 2015  
R. Herbst et al, The Lancet December 2015  
A. Rittmeyer et al, The Lancet January 2017
Toxicity of immune checkpoint blockade

Anti-PD-L1 better than anti-PD1?

R. Pillai et al, Cancer 2017

<table>
<thead>
<tr>
<th></th>
<th>PD-1 Inhibitors</th>
<th>PD-L1 Inhibitors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AEs, %</td>
<td>64</td>
<td>66</td>
<td>.8</td>
</tr>
<tr>
<td>Grade 3-5 AEs, %</td>
<td>13</td>
<td>21</td>
<td>.15</td>
</tr>
<tr>
<td>Fatigue of any grade, %</td>
<td>19</td>
<td>21</td>
<td>.4</td>
</tr>
<tr>
<td>Diarrhea of any grade, %</td>
<td>9</td>
<td>12</td>
<td>.4</td>
</tr>
<tr>
<td>Rash of any grade, %</td>
<td>9</td>
<td>7</td>
<td>.8</td>
</tr>
<tr>
<td>IRAEs, %</td>
<td>16</td>
<td>11</td>
<td>.07</td>
</tr>
<tr>
<td>Grade 3-5 IRAEs, %</td>
<td>3</td>
<td>5</td>
<td>.4</td>
</tr>
<tr>
<td>Hypothyroidism of any grade, %</td>
<td>6.7</td>
<td>4.2</td>
<td>.07</td>
</tr>
<tr>
<td>Pneumonitis of any grade, %</td>
<td>4</td>
<td>2</td>
<td>.01</td>
</tr>
<tr>
<td>Colitis of any grade, %</td>
<td>1.7</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Overall response rate, %</td>
<td>19</td>
<td>18.6</td>
<td>.17</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; IRAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
Toxicity of immune checkpoint blockade

**Anti-PD-L1 better than anti-PD1?**

<table>
<thead>
<tr>
<th>Drug</th>
<th>AE Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>62</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>67.5</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>65</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>75</td>
</tr>
<tr>
<td>Avelumab</td>
<td>67</td>
</tr>
</tbody>
</table>

R. Pillai et al, Cancer 2017
The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Select AEs generally resolved within several weeks, apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy.

Weber et al, ASCO 2015

onset and resolution of select nivolumab-related AEs (any grade)
Toxicity of PD1/PDL1 checkpoint blockade time to onset and resolution

- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs.

Circles represent median; bars signify ranges.

Weber et al. ASCO 2015

onset and resolution of select nivolumab-related AEs (any grade; n=474)
Toxicity of PD1/PDL1 checkpoint blockade
time to onset and resolution

Pembrolizumab:
Immune-mediated Adverse Reactions
Median Time to Onset and Median Duration\(^1\)

- Median time to onset and median duration of immune-mediated adverse reactions are presented based on 2799 patients with NSCLC and melanoma treated with Pembrolizumab

**Median Time to Onset**
- Pneumonitis: 3.3 months (2 days–19.3 months)
- Colitis: 0.5 months (10 days–16.2 months)
- Hepatitis: 1.3 months (8 days–21.4 months)
- Hypophysitis: 4.7 months (1 day–11.9 months)
- Hyperthyroidism: 1.4 months (1 day–21.9 months)
- Hypothyroidism: 1.5 months (1 day–18.9 months)
- Nephritis: 0.1 months (12 days–12.8 months)

**Median Duration**
- Pneumonitis: 1.5 months (1 day–17.2 months)
- Colitis: 1.3 months (1 day–8.7 months)
- Hepatitis: 1.8 months (8 days–20.9 months)
- Hypophysitis: 4.7 months (8 days–12.7 months)
- Hyperthyroidism: 2.1 months (3 days–15.0 months)
- Hypothyroidism: NR (2 days–27.7 months)
- Nephritis: 3.3 months (12 days–8.9 months)

Toxicity of immune checkpoint blockade
Management guidelines

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy:
ESMO Clinical Practice Guidelines for diagnosis,
treatment and follow-up†

J. B. A. G. Haanen,1 F. Carbonnel,2 C. Robert,3 K. M. Kerr,4 S. Peters,2 J. Larkin5 & K. Jordan7, on behalf of the ESMO Guidelines Committee*

The ION-Ghent guidelines for the management of immune related adverse events (irAE’s)

V. Kruse, MD, PhD, M. Schewe, MD, K. Vermaelen, MD, PhD, P. Ost, MD, PhD, T. Kerre, MD, PhD, B. De Moerloose, MD, PhD, L. Brochez, MD, PhD

SUMMARY
Checkpoint inhibitors targeting CTLA-4, PD1 and PD-L1 have become a part of the daily clinical practice in the management of stage IV melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and Hodgkin-lymphoma patients. While these agents can elicit strong anti-tumour immune responses, they can also generate immune related adverse events, which can become life threatening if not detected and managed promptly. At the University Hospital Ghent, we created a working group of organ specialists with specific experience in dealing with immune related adverse events. This initiative is part of ION (Immuo-Oncology-Network) Ghent. In this paper we would like to share our institutional guidelines for the clinical care of patients treated with checkpoint-inhibitors with the Belgian Oncology Community.

(BELG J MED ONCOL. 2017;11(6):265-276)
Pneumonitis under PD-1/PD-L1 blockade management recommendations

**AWARENESS**

- PREVENT
- DETECT
- TREAT

**PREVENT**
- Know the immune-toxicity spectrum
- Identify dysimmunity risk factors
- Inform patients and their healthcare providers

**DETECT**
- Baseline values = reference values
- Eliminate progression
- Always consider dysimmune toxicities

**TREAT**
- Symptomatic treatment
- Patient information
- Discuss:
  - Immunotherapy suspension?
  - Refer to organ specialist?
  - Corticosteroids?
  - Other immunosuppressive drugs?

Champiat et al, Ann Oncol 2016
**Toxicity of immune checkpoint blockade**

**Management guidelines**

- **Grade 1**: Continue ICI
  - Close follow-up

- **Grade 2**: ICI on hold
  - Close follow-up
  - Restart ICI when toxicity ≤ grade 1

- **Grade 3**: ICI on hold + immunosuppressive therapy
  - Taper down immunosuppressive therapy
  - Assess the risk of restarting ICI
  - Close monitoring for relapse

- **Grade 4**: ICI permanent STOP + immunosuppressive therapy
  - Slowly taper down immunosuppressive therapy
  - Close monitoring for relapse

---

**FIGURE 2.** Treatment principles of irAE management. V. Kruse et al, BJMO 2017

**REFER QUICKLY TO RELEVANT ORGAN SPECIALIST**

© K. Vermaelen 2018
Pneumonitis under PD-1/PD-L1 blockade
management recommendations
Pneumonitis under PD-1/PD-L1 blockade
management recommendations
Toxicity of PD1/PDL1 checkpoint blockade
Do steroids jeopardize tumor control?

Ipilimumab (melanoma)
survival vs corticosteroid use for irAEs

T. Horvat et al, J Clin Oncol 2015
Toxicity of PD1/PDL1 checkpoint blockade
Do steroids jeopardize tumor control?

Pembrolizumab (phase I) survival and corticosteroid use for irAEs

N. Leighl et al, WCLC 2015
Toxicity of immune checkpoint blockade
Quid pre-existing auto-immunity?

NB: patients with a history of auto-immune disease were systematically excluded from trials with checkpoint blockers

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Prev (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>5.9</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2.8</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>1.8</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>1.0</td>
</tr>
<tr>
<td>SLE</td>
<td>0.9</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>0.8</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>0.8</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>0.6</td>
</tr>
<tr>
<td>Regional enteritis</td>
<td>0.5</td>
</tr>
<tr>
<td>Ménière's disease</td>
<td>0.5</td>
</tr>
<tr>
<td>Total (any auto-immune disease)</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Prevalence of auto-immune diseases in NSCLC population (SEERS)
S. Khan, ASCO 2016
Toxicity of immune checkpoint blockade
Quid pre-existing auto-immunity?

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab
Menzies et al, Ann Oncol Sep 2016

<table>
<thead>
<tr>
<th>Flare AD on PD1</th>
<th>Number (%) (N = 52)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>32 (62%)</td>
<td>7/13 RA, 3/3 PMR, 1/2 scleroderma, 2/2 Sjogren's, 1/2 psoriatic arthritis</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (19%)</td>
<td>3/6 psoriasis</td>
</tr>
<tr>
<td>Time to flare, median (range), d</td>
<td>38 (8–161)</td>
<td></td>
</tr>
<tr>
<td>Grade of flare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1-2</td>
<td>17 (33%)</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>0 (0%)</td>
<td>1/4 Graves</td>
</tr>
<tr>
<td>Flare by AD subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>14 of 27 (52%)</td>
<td>2/2 ITP</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>3 of 8 (38%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0 of 6 (0%)</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>0 of 5 (0%)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>1 of 4 (25%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>0 of 2 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 of 2 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

38% flare of auto-immune disease
8% permanent discontinuation due to flare
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

baseline 12 weeks today
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 12
Pneumonitis

**Grade**

1: asymptomatic, chance finding on imaging

2: symptomatic, limited impact on ADL

3: significant impact on ADL, hypoxia with monitoring need

4: life-threatening respiratory deterioration

**Management**

- monitor closely
  - Complete diagnostic workup (HRCT, PFT, FB)

- therapy on-hold
  - Complete diagnostic workup (HRCT, PFT, pAO2, FB)
  - Start systemic corticosteroids (methylprednisolone 32 mg/d) + antibiotics (while waiting microbiological test results)

- admit to hospital for monitoring and supportive measures (O2)
  - permanent therapy STOP
  - Complete diagnostic workup
  - Start high-dose systemic steroids (methylprednisolone 64 mg/d) + antibiotics

- admit to ICU
  - permanent therapy STOP
  - Complete diagnostic workup (HRCT, pAO2, FB)
  - Start high dose systemic steroids (methylprednisolone 64 mg/d) + antibiotics

**Treatment and follow-up**

- If imaging or PFT worsens (regardless of symptoms), treat as grade 2

- With regression to grade 1 or less, taper down steroids (max. -8 mg MDP/week)
  - Restart ICI when steroid dose <8 mg MDP/day, monitor closely
  - If pneumonitis relapses: stop ICI permanently

- With clinical improvement, decrease steroids to 32 mg MDP daily, then slowly taper until grade 1 or less
  - Combine with PJP prophylaxis (TMP/SMX 3x/week)
  - Be alert for fungal infections under prolonged corticosteroid therapy
  - Be alert for pneumonitis relapse

- as for grade 3

Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 12

- no symptoms
- WHO PS 0-1
- DLCO dropped 61% → 48%
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 12

- no symptoms
- WHO PS 0-1
- DLCO dropped 61% → 48%
- BAL negative for infection (full of CD8+ lymphocytes!)
- strictly taken: CTC grade 1
- we suspended ICI infusions
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 20

- slight increase in dyspnea
- DLCO dropped 48% → 41%
- **start steroids** (MDP 1mg/kg/d 5 days then taper)
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 28

- after steroid taper to 4 mg/d
- complete clinical and radiographic resolution
- DLCO back to 51%
- anti-PDL1 therapy restarted
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 30

- 2 weeks after ICI restart
- dyspnea recurs
- DLCO dropped to 39%
- relapse pneumonitis gr.2
- restart steroids (MDP 0.5 mg/kg/d 5 days then taper)
- permanently stop ICI
- ➔ clinical and radiographical resolution (DLCO up to 49%)
Case: metastatic NSCLC 3rd line anti-PDL1 therapy in clinical trial

week 40

- = 2 months off-drug
- dyspnea recurs
- DLCO dropped to 38%
- relapse pneumonitis gr.2
- restart steroids (MDP 0.5 mg/kg/d 5 days but slower taper)
- \(\rightarrow\) complete and stable resolution
- \(\rightarrow\) near complete tumor response
Pneumonitis under PD-1/PD-L1 blockade

severity grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pneumonitis: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental activities of daily living (ADL)</td>
</tr>
<tr>
<td>3</td>
<td>Severe symptoms; limiting self-care or activities of daily living, and/or oxygen indicated</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

A, B. Pneumonitis with a cryptogenic organizing pneumonia (COP) pattern

C, D. Pneumonitis with a non-specific interstitial pneumonia (NSIP) pattern

E, F. Pneumonitis with a hypersensitivity pneumonitis (HP) pattern

G, H. Pneumonitis with an acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern
Pneumonitis under PD-1/PD-L1 blockade
radiological patterns
S. Gettinger et al, ASCO 2016

Type 1
Organizing Pneumonia

Type 2
Ground Glass

Type 3
Nodular

Peri-Tumoral Pneumonitis

! aggravation of pre-existing lymphangitis
Pneumonitis under PD-1/PD-L1 blockade
radiological patterns

14d steroids 2 mg/kg/d tapered
Pneumonitis under PD-1/PD-L1 blockade
pathophysiology and predisposing factors

- histopathology: lymphocytic alveolitis
  /organizing pneumonia
- OP component may explain pneumonitis flare upon steroid taper
- more extensive pneumonitis in lung cancer patients ... predisposing immunological terrain?
  - COPD
  - previous radiotherapy
  - undocumented ILD
  - airway microbiota?

M. Nishino et al, ASCO 2016
Pneumonitis under PD-1/PD-L1 blockade: prognostic significance

Table 3: Tumor Response to PD-1 Axis Inhibitor Therapy (RECIST) in Patients with Pneumonitis

<table>
<thead>
<tr>
<th>Response</th>
<th>Objective Response Rate, % (n/N)</th>
<th>Complete Response, n (%)</th>
<th>Duration of response, months*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52 (13/25)</td>
<td>3 (12)</td>
<td>3+ (ongoing), 6, 7, 9+, 10, 13, 13, 37+, 40, 44+, 55+; two patients died from other causes with ongoing response at 4 and 36 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial Response, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stable Disease, n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Progressive Disease n (%)**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Survival</th>
<th>Progression Free, median, days</th>
<th>244</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall, median, days</td>
<td>786</td>
</tr>
</tbody>
</table>

* 5 patients who discontinued PD-1 axis inhibitor therapy for pneumonitis had ongoing tumor response 12, 30, 47, 28 and 35 months, respectively, after their last dose of PD-1 axis inhibitor. The latter 2 patients were not treated with corticosteroids (both grade 1). A 6th patient treated with corticosteroids developed recurrence at one site 26 months after her last dose of PD-1 axis inhibitor therapy.

** One patient with progression as best response had 49% decrease in tumor target lesions (but new lesion), and continued therapy for 11 ½ months with overall survival of 25 months.

S. Gettinger et al, ASCO 2016
Immune-related pneumonitis
• In grade 1 and 2 pneumonitis, interrupt ICPi therapy, try to rule out infection and start with prednisone 1–2 mg/kg orally. Taper over 4–6 weeks [IV–V, B].
• In grade 3 and 4 pneumonitis, discontinue ICPi permanently, admit the patient to the hospital, even ICU if necessary and immediately start high-dose (methyl)prednisone 2–4 mg/kg/6 weeks [IV–V, B].

Add infliximab,

**TNF-blockade**
• Increases risk for pulmonary opportunistic infections, including PJP
• Can by itself induce auto-immune reactions
• Is a biological known to trigger pneumonitis

Toxicity of PD1/PDL1 checkpoint blockade
Quid steroid-refractory pneumonitis?

### Table 1: Summary of FDA-approved TNF-targeted therapies.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Mechanism of action</th>
<th>Usual dosing</th>
<th>FDA-approved indications (approved label as of 1/08)</th>
<th>Non-infectious pulmonary adverse events reported in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept, Enbrel®</td>
<td>Human recombinant form of 2 of human p75 soluble TNFRs fused to the Fc fragment of human IgG1</td>
<td>Binds soluble and cell-bound TNF with high affinity (competitively inhibits binding to TNFRs)</td>
<td>25 mg SC twice weekly or 50 mg SC weekly</td>
<td>Ankylosing spondylitis, Juvenile rheumatoid arthritis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis</td>
<td>Non-caseating granuloma, Interstitial lung disease, Autoimmune disease, Accelerated nodulosis (in patients with rheumatoid arthritis)</td>
</tr>
<tr>
<td>Infliximab, Remicade®</td>
<td>Human IgG1, spliced to the murine human monoclonal anti-TNF antibody</td>
<td>Binds soluble and cell-bound TNF</td>
<td>3 mg/kg (in 0.9% normal saline) IV over 2 h every 8 weeks</td>
<td>Ankylosing spondylitis, Crohn’s disease, Psoriatic arthritis, Plaque psoriasis, Rheumatoid arthritis, Ulcerative colitis</td>
<td>Interstitial lung disease, Exacerbation of underlying lung disease, Precipitation of methotrexate pneumonitis, Diffuse alveolar hemorrhage (37), Autoimmune disease, Interstitial lung disease, Autoimmune disease, Exacerbation of underlying lung disease</td>
</tr>
<tr>
<td>Adalimumab, Humira®</td>
<td>Human recombinant IgG1 monoclonal TNF antibody</td>
<td>Blocks interactions of TNF with the p55 and p75 cell surface TNFRs</td>
<td>40 mg SC every other week</td>
<td>Ankylosing spondylitis, Crohn’s disease, Psoriatic arthritis, Rheumatoid arthritis</td>
<td></td>
</tr>
</tbody>
</table>

TNFR = TNF receptor.

Toxicity of PD1/PDL1 checkpoint blockade

Quid steroid-refractory toxicity?

- corticosteroid doses
- fungal load
- clinical threshold

TNF-blockers for steroid-refractory pneumonitis?

- a lung is not a colon
- zero published evidence for efficacy
- potentially lethal
- AVOID USE
Immune-related toxicities

- occur frequently (all organs/all grades taken together)
- severe grades are rare
- can occur at any time
- can flare up after treatment stop
Immunotherapy for NSCLC
toxicities take home messages

- Corticosteroid use for irAE does not seem to jeopardize long-term anti-tumoral efficacy of checkpoint inhibitors

- irAEs such as pneumonitis may be associated with higher response rates
Immunotherapy for NSCLC
toxicities take home messages

- steroid-refractory irAEs: little evidence regarding rational choice of alternative immuno-suppressive agent

- Avoid TNF-blockade in steroid-refractory pneumonitis!
Mild checkpoint inhibitor rash can be treated with topical corticosteroids.

Diarrhea and Colitis

Slangen et al., World J Gastrointest Pharmacol Ther, 2013

Pneumonitis

3/30/2011

2/21/2011

Two doses of ipilimumab and four of nivolumab

Immunotherapy for NSCLC toxicities take home messages

- have a good baseline (PFT, LFT, creat/ureum, TSH/FT4, LH/FSH/ACTH/cortisol) also TST/IGRA
- be alert (new-onset dyspnea, abdominal pain, asthenia)
- start early with steroids in patients with limited cardiopulmonary reserve

AWARENESS
thanks for your attention!